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Short Communication

Determination of bromine traces in sodium diclofenac, using X-ray fluorescence spectroscopy*

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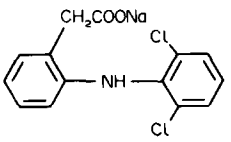
Introduction

The quality control of pharmaceutical products requires techniques of high sensitivity and good accuracy since even traces of impurities can significantly impair their pharmacological profile. In this paper we report a study on sodium diclofenac (**I**), a non-steroidal anti-inflammatory drug [1], widely used in therapy.



(I)

(2 – [(2,6 – Dichlorophenyl) amino] phenyl – acetic acid sodium salt)

The authors believe that commercial diclofenac to be used in pharmaceutical formulations should not contain more than 100 ppm of organic bromine which is a potential impurity arising from the synthetic procedure. Hence, the need for a reliable and sensitive assay of bromine in (**I**). Numerous assay methods for bromides have been described in the literature. For instance, the classical titration according to Volhard's procedure has been prescribed by the FU [2] and BP [3] and by AOAC [4] for the determination of bromine in drugs. On the other hand, more sensitive techniques have been proposed for bromine assays in biological materials or in other matrices, among them electrochemical procedures [5, 6], colorimetric procedures [7–10], instrumental neutron activation analysis [11], high-performance liquid chromatography [12], gas chromatography [13] and ion chromatography [14]. These are unfortunately fairly involved, since they often call for a preliminary mineralization of the samples, when an organic matrix is present. A very interesting technique is X-ray fluorescence spectroscopy on liquid samples which has been reported for the bromide assay in blood serum [15].

The present paper describes a procedure for bromine assay in sodium diclofenac, based on the use of X-ray fluorescence (XRF) spectroscopy on solid samples. This procedure allows the determination of the total bromine content, irrespective of the molecular form in which the element is present, without requiring any solubilization or any other pretreatment of the sample.

Experimental

Apparatus

A Philips PW1450 manual X-ray spectrometer was employed, with W target tube operating at 50 kV and 40 mA, analysing crystal LiF (220) and scintillation counter as detector. A laboratory ball mill Retsch and a Planetary powder mixer Turbula, type T2C were used.

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Materials

Sodium bromide and H_3BO_3 of analytical grade were obtained from C. Erba (Italy). The diclofenac samples were supplied by Prosintex s.p.a. (Italy).

Preparation of standards

Standard samples were prepared both in diclofenac matrix and in H_3BO_3 matrix. They contained NaBr in the low level concentration range 10–250 ppm and the higher level concentration range 250–8000 ppm, in order to cover the relevant low or high level ranges in the unknown samples.

Keeping in mind the need of a constant and homogeneous granulometric distribution, the preparation was effected in the following way:

(a) separate portions of diclofenac and NaBr were ground in a mortar and subsequently pulverized in an agate ball mill. Finally, a given quantity of NaBr was weighed and added to a weighed quantity of diclofenac using the method of geometric dilutions and mixing very thoroughly. The planetary powder mixer was then utilized to perfect the mixing process. The homogeneity of powder obtained was controlled under the microscope.

(b) The same procedure described under (a) was repeated utilizing H_3BO_3 instead of diclofenac.

Procedure

Pellets of samples, one inch in diameter, were obtained by pressing 0.500 g of the standards prepared at 9 ton cm^{-2} over an H_3BO_3 support, according to the procedure described by Volborth [16].

The pellets thus obtained were introduced into the XRF spectrometer and the intensities of the lines emitted at the angles characteristic of the K_α bromine line (λ = 1.041 Å) were measured. The angle was chosen according to the Bragg's diffraction law $2d_{hkl} \sin \Theta = \lambda$, where d_{hkl} is the distance between lattice planes (hkl) in the analysing crystal, Θ is the incident and reflected angle of the X-ray beam to the lattice planes, and λ is the wavelength. All the fluorescence values utilized for both the calibration curves were obtained from probes repeated for two different samples, and for each sample the average of three readings was taken (reading time = 10 s). An identical procedure for sample preparation and spectroscopic measurements was followed in the case of the commercial samples of diclofenac investigated.

Results and Discussion

The presence of bromine, under the conditions described, shows up in the form of maxima of radiation emitted at $2\Theta = 42.88°$ (K_α) and $2\Theta = 38.25°$ ($K_{\beta_{1,3}}$), in agreement with Bragg's law using LiF (220) analysing crystal, where $2d_{220}$ = 2.848 Å. The K_α radiation was selected for the determination of bromine in diclofenac, due to a better sensitivity.

In Fig. 1 the XRF spectrum obtained from an impure sample of diclofenac (B^I) is reported, along with those of bromine-free diclofenac and bromine-free boric acid for comparison. In order to construct the calibration curves, synthetic standards were prepared adding NaBr powder to bromine-free sodium diclofenac. The purity of the product was assayed comparing the fluorescence data obtained by a diclofenac sample C^I with those obtained from pellets of bromine free boric acid. In both cases the Br K_α peak could not be detected in the background (Fig. 1), the net peak intensity (after subtracting the background) only amounted to a few counts per second (cps), and was invariably lower than $3\sqrt{N_B}$ (where N_B is the background intensity), i.e. the minimum limit of detection.

Since the background measured with diclofenac was lower than that of boric acid, any presence of bromine impurities should be better detectable in the first compound. Adding to both products 10 ppm NaBr (7.7 ppm bromine), it was possible to enhance the $K\alpha$ Br peak, but still the net intensity was on the borderline of detectability. For this reason and due to the high counting error typical of very low contents, the value of 7 ppm for bromine was chosen as the lower limit of detection.

Two calibration curves were constructed, for low and high bromine levels (7.7–194 and 194–6200 ppm bromine, respectively), by plotting the values of net intensity of XRF, expressed in cps, against the NaBr concentration, expressed in ppm. They showed good linearity over the range 10–250 ppm NaBr ($y = 0.0218x + 1.8663$; $r_c = 0.9998$) and over the range 250–8000 ppm NaBr ($y = 0.0268x + 2.7234$; $r_c = 0.9999$). The precision was good, varying from 1% at 1000 ppm to 3% at 20 ppm.

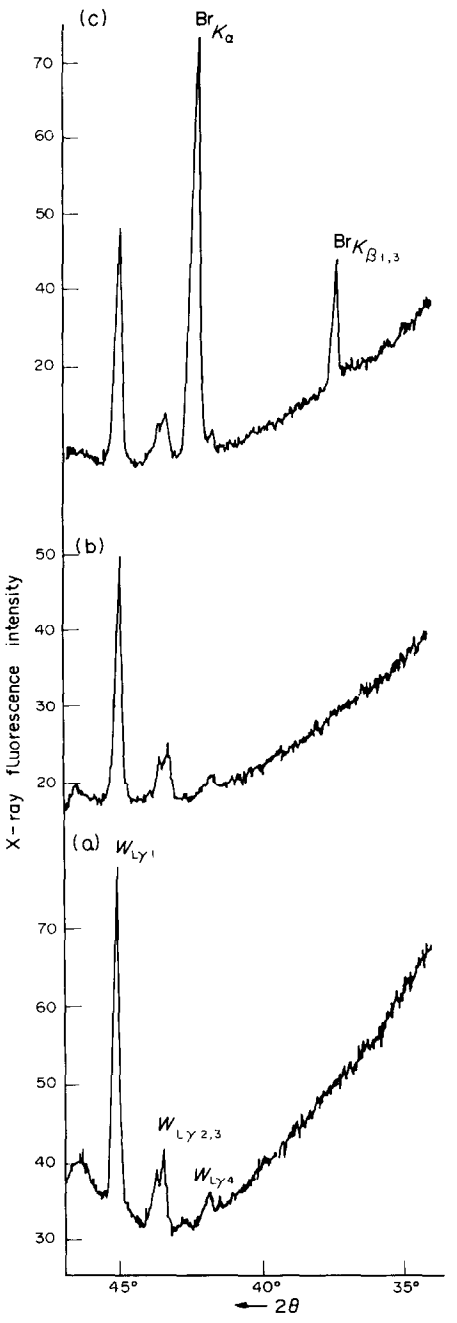

Figure 1
X-ray fluorescence spectra of: (a) an H_3BO_3 sample; (b) a pure diclofenac sample (C'); (c) a diclofenac sample containing bromine impurities (B'). Experimental conditions: 4×10^3 cps (counts per second); time constant = 1; goniometer scan = 1 deg min^{-1}.

The stability of the pellets of the standards of NaBr in diclofenac was good; these pellets remained unchanged for some months, allowing the readings of XRF intensity data of standards and therefore their utilization for new samples of diclofenac. The method has been applied to the analysis of bromine in

Table 1

Samples	Source	Bromine (ppm)
A^I	Far East	4650
A^{II}	Far East	4867
A^{III}	Far East	6177
A^{IV}	Far East	4656
B^I	Europe	470
B^{II}	Europe	390
B^{III}	Europe	1740
C^I	Italy	<10
C^{II}	Italy	<10
C^{III}	Italy	<10

Assay results for bromine impurities in diclofenac samples supplied by Prosintex by means of XRF.

diclofenac samples from different countries. The intensity XRF data obtained have been used for bromine determination from the appropriate calibration curve, and they are reported in Table 1. As the table clearly shows, a considerable variety of impurity ranges were observed in the different samples examined, which might be related to the different synthetic routes utilized.

In order to assay the applicability of the XRF method to products of different composition, calibration curves were also obtained for mixtures, containing NaBr in H_3BO_3 matrices at concentrations within the ranges quoted above. These calibration curves were applied to a check of the assay results of bromine in diclofenac previously obtained. The consistently lower values observed (~60%) are a clear indication of a matrix effect.

Investigations aimed at the circumvention of this problem are presently under way. A first result towards its solution is the utilization of the background as internal standard. Indeed calibration curves in which the ratio "net intensity/background intensity" is plotted against concentration have given compatible results for standards of diclofenac as well as for those in H_3BO_3, over the range 250–8000 ppm NaBr.

Conclusions

The method proposed, based on the use of XRF spectroscopy on solid samples, appears suitable, in terms of feasibility and sensitivity, for the determination of bromine impurities in commercial samples of sodium diclofenac. Advantages of the procedure are the ease and speed of analysis, the possibility to utilize

samples without special pretreatments or solution preparation, and the long term stability of pellets, both of standards and of samples, which allows long delays between calibration and analysis. Another advantage lies in the fact that XRF is an elemental technique, capable of detecting bromine in whatever form it is present without requiring any hypothesis on the nature of the molecule containing it. On the negative side one might mention the fact that the homogenization of standards is fairly laborious, especially for low bromine levels and the fact that the method, although very promising, still suffers from the "matrix effect".

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